Remarks

Claims 1-117 and 121-127 are pending. Claims 1-97, 111-117 and 121-124 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 118-120 have been canceled. Claims 98 and 105 have been amended. Support for these amendments can be found in original claim 1, and in the specification on page 40, lines 11-25, and in the specification on page 87, lines 3-6. Support for newly added claims 125 and 127 can be found in original claims 48 and 53, respectively. Support for newly added claim 126 can be found in the specification on page 40, lines 19-25. Applicants submit that no new matter was added.

Claim Objections

Claims 98, 105, and 118 are objected to for depending from a withdrawn claim. Claim 118 has been canceled. Applicants have amended claims 98 and 105 to incorporate the limitations of claim 1 from which they depended. Therefore, applicants respectfully request the withdrawal of this objection.

Claim 118 is objected to for missing the word "is". Claim 118 has now been canceled. Therefore, applicants respectfully request the withdrawal of this objection.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 98-104 has been rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for inducing an immune response comprising contacting a B

lymphocyte cell *in vitro* with a chimeric protein comprising activation induced deaminase (AID), allegedly does not reasonably provide enablement for inducing an immune response comprising contacting a B lymphocyte cell *in vivo* with a chimeric protein comprising activation-induced deaminase (AID), or with any other deaminase chimera. Applicants respectfully traverse. However, in an effort to expedite prosecution, applicants have amended claim 98 to recite that the cells are treated *ex vivo*, and have canceled claims 99 and 100. Applicants therefore respectfully request withdrawal of this rejection.

Regarding claims 105-110, the Office Action alleges that the disclosure fails to provide any working embodiments that meet the claimed limitations. The Office Action states: "While there are examples that characterize the structures and functions of various deaminases, namely CEM15, ARP1, Cddl, AID, APOBEC1 and its related proteins by structural comparison and activity assays and methods for identifying inhibitors, they do not relate to contacting B lymphocytes in vitro or in vivo and measuring the amount of immune response in the B cells, let alone the treatment of hyper-lgM syndrome and B cell lymphoma. No in vivo working example of B cell contacting is disclosed in the specification." Applicants respectfully traverse. However, in an effort to expedite prosecution, applicants have amended claim 105 to recite that the deaminase is AID, and that the method is carried out *ex vivo*. Therefore, applicants respectfully request withdrawal of this rejection.

Regarding the rejection of claims 118-120, these claims have now been canceled. The withdrawal of the rejection of these claims is therefore respectfully requested.

For all of the above reasons, Applicants submit that no proper prima facie case of lack of written description has been established. Applicants therefore respectfully request the withdrawal of this rejection.

Rejection Under 35 U.S.C. § 103

Claims 98, 99 and 101-104 are rejected under 35 U:S.C. §103(a) as being unpatentable over Martin et al. (2002, No. A227 in the IDS filed on 08 December 2005) in view of Schwarze et al. (2000, No. A305 in the IDS filed on 08 December 2005) and Sutkowski et al. (1994). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Office Action alleges that Martin et al. disclose contacting three human B cell lines, Ramos, BL-2 and CL-01, respectively, with vectors expressing human activation-induced cytidine deaminase (AID). Martin et al disclose that hybridomas (antigen-challenged B cells fused with myeloma tumor cells that can grow indefinitely in culture) can be induced to undergo high rates of somatic hypermutation with expression of AID to obtain subclones that produce high-affinity monoclonal antibodies and/or antibodies that are more specific. Applicants respectfully traverse this rejection. The methods taught by Martin et al. are very different than those of the present claims, namely, contacting a B lymphocyte cell with a *chimeric protein* comprising AID. The methods of Martin et al. are simply drawn to expressing the AID molecule

in vitro. In fact, Martin et al. states that, "the exact role [of AID] is unknown.] Simply knowing that expression of AID would lead to somatic hypermutation is vastly different from inducing an immune response in a subject by subjecting the cells *ex vivo* to a chimeric protein.

Schwarze et al does not make up for this deficiency. Schwarze et al. is relied upon to show that TAT can allow for transduction of a protein across a cell. However, one of skill in the art would not have thought that combining a protein transduction domain such as TAT and AID would have yielded a functional AID molecule that was able to not only transduce the cell, but be properly re-folded, and retain the ability induce an immune response in a subject. One of skill in the art would not have supposed that AID could have retained such functionality when coupled to TAT based on the teachings of Schwarze et al. and Martin et al.

The Office Action then relies upon the art of Sutkowski et al., which discloses injecting deaminase-expressing B-lymphocyte cells into mice intravenously. Again, this is very different than the claimed *ex vivo* methods. The Office Action argues that there would have been a reasonable expectation of success, given it is known in the art that TAT-PTD fusion proteins can transduce different proteins into all cell types and yield biological activity, as taught by Schwarze et al, and given that it is long been known in the art to contact B lymphocyte cells with a therapeutic protein *in vitro* and subsequently introduce the B cells into the subject, as shown by Sutkowski et al. Applicants respectfully traverse. First of all, Schwarze et al. does not show that, as the Office Action alleges, "TAT-PTD fusion proteins can transduce different proteins into all cell types and yield biological activity." The teaching of

Schwarze et al. is a β-galactosidase molecule only, which is quite different than inducing an immune response in a subject with the use of a complex molecule such as AID. Martin et al. shows only that somatic hypermutation occurs when a cell is contacted *in vitro* with an AID molecule, and Sutkowski doesn't mention the AID molecule at all, but instead discusses the exogenous transfer of genes to B cells.

According to the MPEP, evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). See also *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1207-08, 18 USPQ2d 1016, 1022-23 (Fed. Cir.), *cert. denied*, 502 U.S. 856 (1991). In this case, due to the very complex nature of the AID molecule, and the state of the art at the time of filing regarding TAT, no one in the art would have supposed that an immune response could have been elicited in a subject by coupling TAT to AID, and introducing it to a subject *ex vivo*.

Applicants assert that no combination of the art and/or the knowledge generally available to those of skill in the art at the time the application was filed provides a reasonable expectation of success. The MPEP (Section 2143.02) states that "A rationale to support a conclusion that a claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art." *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1395 (2007); *Sakraida v. AG Pro, Inc.*, 425 U.S. 273, 282, 189 USPQ 449, 453

(1976); *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57, 62-63, 163 USPQ 673, 675 (1969); *Great Atlantic & P. Tea Co. v. Supermarket Equipment Corp.*, 340 U.S. 147, 152, 87 USPQ 303, 306 (1950). Applicants again submit that the art cited in the Office Action hardly reaches the threshold of "yielding nothing more than predictable results," as discussed above.

For at least these reasons, Applicants respectfully request the withdrawal of this rejection.

Conclusions

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A credit card payment submitted via EFS Web in the amount of $230.00, representing the fee for a small entity under 37 C.F.R. § 1.17(a)(2), and a Request for Extension of Time are enclosed. This amount is believed to be correct; however, the Commissioner is hereby

authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.

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CERTIFICATE OF EFS-WEB TRANSMISSION UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as attached or included, is being transmitted by EFS-WEB on the date indicated below.

/Janell T. Cleveland/ — July 15, 2008

Janell T. Cleveland — Date